

We claim:

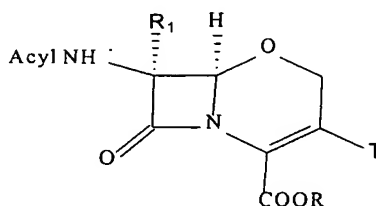
1. A method of treatment of a behavioral disorder selected from aggressive disorder, obsessive-compulsive disorder, anxiety, depression, or ADHD in
5 a patient in need of such treatment, said method comprising the step of administering to said patient an effective amount of a compound capable of inhibiting the peptidase activity of one or more neurogenic peptidases in the brain of said patient.
2. The method of claim 1 wherein the behavioral disorder is depression or obsessive-compulsive disorder.
- 10 3. The method of claim 2 wherein the peptidase inhibitor is administered as an antiaggressive agent to control impulsivity and violence in a human patient afflicted with autism, Tourette's syndrome, mental retardation, psychosis, mania, senile dementia or in a patient with a personality disorder and history of inappropriate aggression.
- 15 4. The method of claim 2 wherein the compound is administered to a human patient suffering a behavioral disorder comprising anxiety.
5. The method of claim 2 wherein the compound is administered to a human patient suffering a behavioral disorder comprising ADHD.
- 20 6. The method of claim 1 wherein the peptidase inhibitor is a β -lactam compound.
7. The method of claim 6 wherein the β -lactam compound is a β -lactamase inhibitor.
8. The method of claim 7 wherein the peptidase inhibitor is selected from the group consisting of penicillins, cephalosporins, penems, 1-oxa-1-dethia cephe-
25 mams, clavams, clavems, azetidinones, carbapenams, carbapenems and carbacephems.
9. The method of claim 9 wherein the peptidase inhibitor is a 1-oxa-1-dethia-analogue of a cephalosporin.
10. The method of claim 1 wherein the compound is a β -lactamase inhibitor.
- 30 11. The method of claim 1 further comprising the step of administering an effective amount of a P-glycoprotein efflux pump inhibitor.

12. The method of claim 6 or claim 7 wherein the peptidase inhibitor is administered in combination with an effective amount of a P-glycoprotein efflux pump inhibitor.

13. The method of claim 1 wherein the peptidase inhibitor is a β -lactam antibiotic and the amount administered to the patient is less than an amount effective to provide antibiotically effective blood levels of the inhibitor.

14. The method of claim 1 or claim 3 wherein the peptidase inhibitor is a compound of the formula

10



15 wherein R is hydrogen, a salt forming group or an active ester forming group; R^1 is hydrogen or C_1 - C_4 alkoxy; T is C_1 - C_4 alkyl, halo, hydroxy, $O(C_1-C_4)$ alkyl, or $-CH_2B$ wherein B is the residue of a nucleophile $B:H$, and acyl is the residue of an organic acid $AcylOH$.

15. The method of claim 14 wherein the compound is moxalactam or flomoxef.

16. The method of claim 1 wherein the peptidase inhibitor is a 2-optionally substituted oxa-2-deamino analogue of glutamic acid, a 2-optionally substituted carba-2-deamino analogue of glutamic acid or an N-substituted derivative of glutamic acid.

17. The method of claim 16 further comprising the step of administering an effective amount of a P-glycoprotein efflux pump inhibitor.

18. A method of enhancing cognitive function in a patient in need of said treatment, said method comprising the step of administering to said patient an effective amount of a compound capable of inhibiting the peptidase activity of one or more neurogenic peptidases in the brain of said patient.

19. The method of claim 18 wherein the warm-blooded vertebrate is a human patient suffering from dementia or amnesia.

20. The method of claim 18 wherein the warm-blooded vertebrate is a human patient suffering from Alzheimer's Disease.

21. The method of claim 18 wherein the peptidase inhibitor is a β -lactam compound.

5 22. The method of claim 21 wherein the β -lactam compound is a β -lactamase inhibitor.

23. The method of claim 21 wherein the peptidase inhibitor is selected from the group consisting of penicillins, cephalosporins, penems, 1-oxa-1-dethia cephems, clavams, clavams, azetidinones, carbapenams, carbapenems and
10 carbacephems.

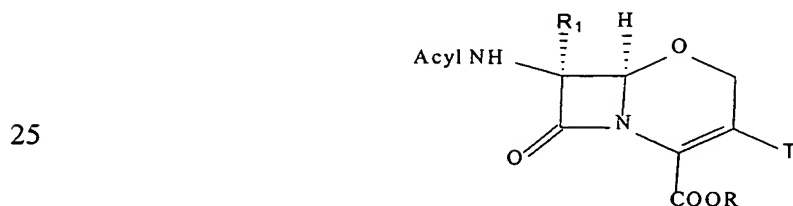
24. The method of claim 23 wherein the peptidase inhibitor is a 1-oxa-1-dethia-analogue of a cephalosporin.

25. The method of claim 18 wherein inhibitor further comprising the step of administering an effective amount of a P-glycoprotein efflux pump inhibitor.

15 26. The method of claim 23 wherein the peptidase inhibitor is administered in combination with an effective amount of a P-glycoprotein efflux pump inhibitor.

27. The method of claim 18 wherein the peptidase inhibitor is a β -lactam antibiotic and the amount administered to the patient is at least 50 $\mu\text{g/kg}$ but less than an amount effective to provide antibiotically effective blood levels of the inhibitor.

20 28. The method of claim 18 wherein the peptidase inhibitor is a compound of the formula



wherein R is hydrogen, a salt forming group or an active ester forming group; R¹ is hydrogen or C₁-C₄ alkoxy; T is C₁-C₄ alkyl, halo, hydroxy, O(C₁-C₄)
30 alkyl, or -CH₂B wherein B is the residue of a nucleophile B:H, and acyl is the residue of an organic acid AcylOH.

29. The method of claim 28 wherein the compound is moxalactam or flomoxef.
30. The method of claim 29 wherein inhibitor further comprising the step of administering an effective amount of a P-glycoprotein efflux pump inhibitor.
- 5 31. The method of claim 18 wherein the peptidase inhibitor is a 2- optionally substituted oxa-2-deamino analogue of glutamic acid, a 2- optionally substituted carba-2-deamino analogue of glutamic acid or an N-substituted derivative of glutamic acid.
- 10 32. The method of claim 34 wherein inhibitor further comprising the step of administering an effective amount of a P-glycoprotein efflux pump inhibitor.
33. A method of treating a human patient afflicted with a condition, or disposed to development of a condition characterized at least in part by abnormal extracellular glutamate concentration in the brain or other nervous tissue, said method comprising the step of administering to said patient a composition comprising a
15 compound capable of inhibiting the activity of a penicillin-binding protein or a β -lactamase of bacterial origin, wherein said composition is administered in an amount effective to prevent or alleviate the damage or symptoms of such condition.
34. The method of claim 33 wherein the compound is a β -lactam compound.
- 20 35. The method of claim 33 wherein the compound is a β -lactamase inhibitor.
36. The method of claim 34 wherein the compound is selected from the group consisting of penicillins, cephalosporins, penems, 1-oxa-1-dethia cephems, clavams, clavems, azetidinones, carbapenams, carbapenems and carbacephems.
- 25 37. The method of claim 36 wherein the compound is a 1-oxa-1-dethia-analogue of a cephalosporin.
38. The method of claim 37 wherein the compound is moxalactam or an orally absorbed active ester thereof.
39. The method of any of claims 33, 34, 35, 36, 37, or 38 wherein the
30 patient condition is selected from the group consisting of ischemia, epilepsy, hypoglycemia, Huntington's disease, Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), chronic pain, and nervous tissue trauma.

40. The method of claim 37 wherein the patient condition is nervous tissue ischemia resulting from a temporary interruption of blood flow to said tissue.

41. A method of treating prostate disease selected from prostate cancer or benign prostatic hyperplasia in a human patient, said method comprising the step of
5 administering to said patient a composition comprising a compound capable of inhibiting the activity of a penicillin-binding protein or a β -lactamase of bacterial origin, wherein said compound is administered in an amount effective to retard the progress of the disease or to reduce the symptoms of the disease.

42. The method of claim 41 wherein the compound is a β -lactam
10 compound.

43. The method of claim 41 wherein the compound is a β -lactamase inhibitor.

44. The method of claim 42 wherein the compound is selected from the group consisting of penicillins, cephalosporins, penems, 1-oxa-1-dethia cephe-
15 mams, clavams, azetidinones, carbapenams, carbapenems and carbacephems.

45. The method of claim 43 wherein the compound is a 1-oxa-1-dethia-analogue of a cephalosporin.

46. The method of claim 44 wherein the compound is moxalactam, an orally absorbed active ester thereof, or a β -lactamase inhibitor.

47. A method for treatment of anxiety disorders in a human patient in need
20 of said treatment, said method comprising the step of administering an inhibitor of a neurogenic peptidase to said patient in an amount effective to modulate neurogenic carboxy peptidase or transpeptidase activity in the brain of said patient.

48. The method of claim 47 wherein the neurogenic peptidase activity is
25 characterized by its inhibition by a peptide comprising the sequence Ala-D- γ -Glu-Lys-D-alanyl-D-alanine.

49. A pharmaceutical formulation for treatment of behavioral or cognitive disorders in a human patient in need thereof in unit dosage form, said formulation comprising a β -lactam compound and a pharmaceutically acceptable carrier therefor,
30 said β -lactam compound in said unit dosage being effective to modulate cognitive and behavioral performance, but without antibiotic efficacy.

50. The pharmaceutical formulation of claim 49 wherein the β -lactam compound is a β -lactam antibiotic, and the amount of said β -lactam antibiotic is less than that capable of producing, upon administration of said formulation, antibiotically effective blood levels of the antibiotic, but in an amount effective to produce levels of the β -lactam antibiotic in the brain sufficient to modulate cognitive and behavioral performance.

51. The pharmaceutical formulation of claim 49 wherein the β -lactam compound is a β -lactamase inhibitor substantially free of a clinically effective β -lactam antibiotic.

52. The pharmaceutical composition of claim 50 wherein the β -lactam antibiotic is a 1-oxa-1-dethia cephalosporin.

53. The pharmaceutical formulation of claim 50 wherein the β -lactam antibiotic is a 7-methoxy-1-oxa-1-dethia cephalosporin.

54. The pharmaceutical formulation of claim 50 wherein the β -lactam antibiotic is moxalactam or an active ester derivative thereof.

55. The pharmaceutical formulation of claim 54 formulated for parenteral administration wherein the antibiotic is moxalactam in an amount corresponding to about 50 μ g/kg to about 400 μ g/kg of patient body weight.

56. The pharmaceutical formulation of claim 53 in an oral dosage form wherein the β -lactam antibiotic is an active ester of moxalactam at about 2.5 to about 250 mg per unit dose.

57. The pharmaceutical composition of claim 50 further comprising an effective amount of a P-glycoprotein efflux pump inhibitor.

58. The pharmaceutical composition of claim 49 further comprising an effective amount of a P-glycoprotein efflux pump inhibitor.

59. The pharmaceutical composition of claim 50 wherein the formulation is an oral dosage form.

60. The pharmaceutical composition of claim 50 wherein the formulation is a parenteral dosage form.

61. The pharmaceutical composition of claim 50 wherein the formulation is a prolonged release dosage form.

62. A method of treating cognitive disorders in a human patient in need of said treatment, said method comprising the step of inhibiting neurogenic peptidase activity in the brain of said vertebrate, said neurogenic peptidase characterized by its inhibition with effective amounts of the peptide Ala-D- γ -Glu-Lys-D-Ala-D-Ala.

5 63. The method of claim 62 wherein the step of inhibiting the neurogenic peptidase is carried out by administering an amount of a β -lactam antibiotic effective to enhance the patient's cognitive performance.

64. The method of claim 63 wherein the β -lactam antibiotic is administered in an amount less than that necessary to obtain antibiotically effective
10 blood levels of said antibiotic.

65. A method of treatment of behavioral disorders in human, canine, feline and equine species, said method comprising the step of inhibiting the activity of a neurogenic peptidase characterized by its inhibition with effective amounts of the peptide Ala-D- γ -Glu-Lys-D-alanyl-D-alanine.

15 66. The method of claim 65 wherein the neurogenic peptidase comprises an N-acetylated- α -linked acidic dipeptidase.

67. The method of claim 65 wherein the step of inhibiting the neurogenic peptidase is effected by administering an amount of a β -lactam compound effective to inhibit activity of the peptidase in the brain.

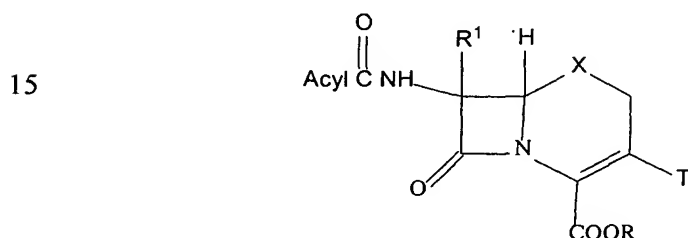
20 68. The method of claim 66 wherein the β -lactam compound is a 1-oxa-1-dethia analogue of a cephalosporin.

69. The method of claim 67 wherein the β -lactam compound is selected from the group consisting of moxalactam, ampicillin and carbenicillin and active esters thereof.

25 70. A method of treatment of a behavioral disorder in human, canine, feline and equine species suffering from said disorder, said method comprising the step of inhibiting the activity of a neurogenic peptidase characterized by its inhibition with a peptide comprising the sequence Ala-D- γ -Glu-Lys-D-alanyl-D-alanine by administering to said vertebrate a β -lactam compound selected from β -lactam
30 antibiotics and β -lactamase inhibitors in an amount effective to inhibit said peptidase activity.

71. A pharmaceutical formulation in oral dosage form for treatment of behavioral or cognitive disorders, said formulation comprising, as a neurologically active ingredient, a β -lactam antibiotic wherein the amount of said antibiotic is less than that capable of providing antibiotically effective blood levels of said antibiotic, and a pharmaceutically acceptable carrier therefor, the amount of said β -lactam antibiotic in said dosage form being effective to provide, upon per os administration of the dosage form to a patient experiencing symptoms of a behavioral or cognitive disorder, a concentration of said β -lactam antibiotic in the brain effective to reduce the patient's symptoms of a behavioral disorder or to enhance cognitive performance in a patient suffering from dementia or amnesia.

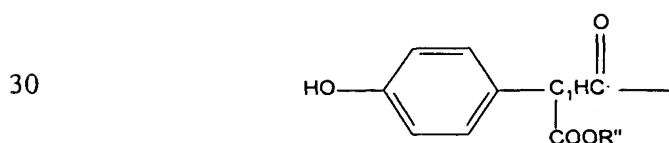
72. The pharmaceutical formulation of claim 71 wherein the β -lactam antibiotic is a compound of the formula



20 wherein X is O, C, or S; R is H or a pharmaceutical acceptable salt-forming or ester-forming group;

acyl is a residue of an organic acid of the formula acyl-OH; R¹ is H or lower alkoxy; and T is OH, Cl, F, Br, I, CH₃, C₂-C₄ alkyl, aryl, including heteroaryl, S-alkyl, S-aryl, including S-heteroaryl, SO₃R (R=H, alkyl, aryl), SO₂R (R=H, alkyl, aryl), N-alkyl₂, N-aryl₂, CO₂R (R=H, alkyl), P-alkyl₂, P-aryl₂, PO₃R₂ (R=H, alkyl, aryl).

73. The pharmaceutical formulation of claim 72 wherein X = O and acyl is a group of the formula



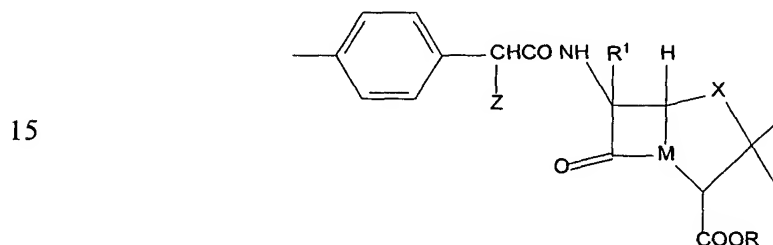
wherein optical center C_1 is in the D form and R is selected from H or a pharmaceutical acceptable salt-forming or ester-forming group.

74. The pharmaceutical formulation of claim 73 wherein R^1 is methoxy and T is 1-methyltetrazol-5-ylthiomethyl.

5 75. The pharmaceutical formulation of claim 74 wherein R is an ester forming group capable of being hydrolyzed *in vivo* to produce the corresponding compound where $R=H$.

76. The pharmaceutical formulation of claim 71 further comprising a P-glycoprotein efflux inhibitor.

10 77. The pharmaceutical formulation of claim 69 wherein the β -lactam antibiotic is a compound of the formula



wherein $X = O, S,$ or C ; R is H or a pharmaceutical acceptable salt-forming or ester-forming group; R^1 is H or lower alkoxy, and G is hydrogen or hydroxy and Z is
20 amino, acylamino, CO_2M , SO_3M , PO_3M_2 or PO_2M wherein M is hydrogen or a pharmaceutically acceptable salt-forming or ester forming group.

78. The use, in the manufacture of a medicament, of an inhibitor of the peptidase activity of a N-acetylated- α -linked-acidic dipeptidase as the active
25 ingredient in a cognition enhancing composition in admixture with a pharmaceutically acceptable carrier.

79. The use, in the manufacture of a medicament, of an inhibitor of the peptidase activity of a N-acetylated- α -linked-acidic dipeptidase as the active
ingredient in an anxiolytic composition in admixture with a pharmaceutically acceptable carrier.

30 80. The use of any of claims 78 or 79 wherein the inhibitor is a β -lactam antibiotic or a β -lactamase inhibitor.

81. The use of claim 80 wherein the medicament further includes a P-glycoprotein efflux pump inhibitor.

82. The use of any of claims 78, 79, or 80 wherein the inhibitor is a 2-optionally substituted oxa-2-deamino analogue of glutamic acid, a 2-optionally substituted carba-2-deamino analogue of glutamic acid, or an N-substituted derivative of glutamic acid.

83. The use of claim 82 wherein the medicament further includes a P-glycoprotein efflux pump inhibitor.

84. A method for treating a patient afflicted with or disposed to develop a disease characterized by abnormally elevated glutamate concentrations in neuronal tissue or elevated NAALADase levels in prostate tissue, said method comprising the step of administering to said patient a compound capable of exhibiting a specific binding interaction with a penicillin binding protein, said compound being administered in an amount effective to inhibit NAALADase activity and thereby reduce or prevent the symptoms of the disease.

85. A method for treating a patient afflicted with multiple sclerosis which method comprises the step of administering to said patient a β -lactam compound, said compound being administered to said patient in an amount effective to inhibit NAALADase activity in the patient's nervous tissue.

86. The method of any of claims 1, 18, 33, 34, 41, 84 and 85 wherein the NAALADase inhibitor is a β -lactamase inhibitor substantially devoid of antibiotic activity.

87. The method of any of claims 1, 18, 33, 35, 41, 84 and 85 wherein the NAALADase inhibitor is a penicillin or cephalosporin sulfoxide or sulfone derivative substantially devoid of antibiotic activity.

88. The method of claim 85 wherein the β -lactam compound is moxalactam or an ester thereof.

89. The use of a β -lactam compound in the manufacture of a medicament for use in the treatment of anxiety without concomitant antibiotic effect.